## REMARKS/ARGUMENTS

Reconsideration of the present application, as amended, is respectfully requested.

### A. STATUS OF THE CLAIMS

As result of the present amendment, claims 1-10, 12-19, 21 and 27 are presented in the case for continued prosecution.

Claim 1 has been amended to eliminate a possibility of prodrugs being a non-polymeric prodrug. Thus, claim 1, as amended herein, is limited to polymeric prodrugs. Additionally, informalities concerning Q" group have been corrected in claim 1.

New claim 27 has been added to clarify polymeric prodrugs corresponding to those of claim 1.

Claim 8 has been amended to clarify a definition of "n" contained in SEQ ID NO: 4.

Claim 9-10 and 13-18 have been amended to conform to claim 1 as amended herein and new claim 27.

Claim 11 has been cancelled without prejudice.

Claim 12 has been amended to include definitions of $R_9$ and Ar groups. Support for the amendments can be found, for example, on page 19, line 25 through page 23, line 10.

Claims 2-3, 5-6, 9, 12-18 and 21 have been amended to change dependency. The claims as amended herein depend from new claim 27.

Withdrawn claims 20 and 22 have been amended to conform to claim 1, as amended herein, and new claim 27.

Withdrawn claim 23 has been amended to depend from claim 27.

No new matter has been added.

### B. CLAIM REJECTIONS UNDER 35 USC 112, SECOND PARAGRAPH

On page 3 of the Office Action, claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite.

The rejection is directed to the recitation of "compatible nucleotide" for "n" contained in SEQ ID NO: 4. The Examiner indicated that the definition of "n" is not recognized in the art.

Without admitting the appropriateness of the Examiner's position and for facilitating prosecution, claim 8 has been amended to remove the recitation of "compatible" for "n". Claim 8, as amended herein, recites that "n is any nucleotide".

The amended definition of "n" corresponds to that in the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings in Patent Applications (1998), ("WIPO Standard ST.25 (1998)"). "WIPO Standard ST.25 (1998)" has been incorporated by reference in CFR 1.821 through 1.825.

Those of ordinary skill in the art can appreciate the definition of "n," which is a standard term of art and conforms to the requirements of the USPTO and PCT rules. Thus, the definition is not indefinite.

Reconsideration and withdrawal of the rejection under 35 USC 112, second paragraph, is respectfully requested.

## C. SUMMARY OF THE INVENTION

The claimed prodrug, as amended herein, is directed to an oligonucleotide-polymer conjugate. The oligonucleotide modified with a C2-C10 carbon-containing bifunctional spacer group is linked to a polymer via a releasable linker. The claimed polymeric prodrugs provide desirable pharmacokinetic characteristics, e.g., improved stability and solubility, to oligonucleotides and means for clinicians to use oligonucleotides as therapeutics in treatment of various diseases.

## D. THE CLAIMS ARE NOT RENDERED OBVIOUS BY TENG IN VIEW OF GREENWALD & DANDLIKER

On pages 3-6 of the Office Action, the Examiner has rejected the subject matter of pending claims under 35 U.S.C. 103(a) as being allegedly unpatentable over Teng et al. (U.S. Patent No. 6,887,906) in view of Greenwald et al. (U.S. Patent No. 6,303,569) and Dandliker et al. (U.S. Patent No. 5,707,813). The Examiner has alleged that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to produce the bcl-2 sequence of Teng in a polymeric prodrug form, as taught by Greenwald et al. The Examiner further alleged that it is obvious to use hexylamine linkers as a component of the polymeric prodrug according to

Dandliker.

Applicants respectfully traverse.

Teng et al. discloses compositions of antisense bcl-2 oligonucleotides. The Examiner indicated that "At column 17, lines 58-67 Teng et al. teach that the oligonucleotides of their invention can be provided in prodrug form, an inactive form that is converted to active form within a cell. Teng at al. do not explicitly teach the use of polymeric prodrugs". See page 4, second paragraph of the Office Action.

The Examiner has taken the position that Greenwald et al. and Dandliker cure the deficiency of Teng et al. Greenwald et al. discloses polymeric prodrugs including a releasable linker. A biologically active agent can be attached to the polymeric prodrugs via the releasable linker such as a trimethyl lock lactonization-based linker.

The Examiner further indicated that "it was well known in the art at the time of invention to employ alkyl linkers as a component of an oligonucleotide conjugate". With respect to the oligonucleotide modified with the alkyl linker, the Examiner relied on Dandliker et al.

Contrary to the Examiner's position, it is respectfully urged that nowhere does Teng and/or the references cited, whether taken alone or in any combination, teach the specific conjugation of a C2-C10 carbon-containing bifunctional spacer-modified oligonucleotide to a polymer via a releasable linker as required in the claimed polymeric prodrugs.

Teng et al teaches delivery of oligonucleotides by the use of compositions containing various fatty acids, bile salts, etc. as main ingredients. The oligonucleotide delivery system of Teng et al. relies on fatty acids, bile salts, chelating agents, etc for enhancing stability and delivery of oligonucleotides. The oligonucleotide delivery system is not based on polymeric prodrugs as required by the claimed invention.

The descriptions at column 17, lines 58-67 of Teng et al., referred to by the Examiner as pertinent to use of prodrugs of oligonucleotides, provide as follows.

> B. Oligonucleotide Prodrugs: The oligonucleotides of the invention may additionally or alternatively be prepared to be delivered in a "prodrug" form. The term "prodrug" indicates a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions. In particular, prodrug versions of the oligonucleotides of the invention are prepared as SATE ((S-acetyl-2-thioethyl) phosphate) derivatives according to the methods disclosed in WO 93/24510 to Gosselin et al., published Dec. 9, 1993.
> Emphasis added.

As shown above, SATE-modified prodrugs prepared as taught by Teng et al. are non-polymeric prodrugs. The modification of WO 93/24510, referred to by Teng et al., is a simple non-polymeric nucleoside modification, for example, nucleoside modification with SATE, $-(CH_2)_n$-S-C(=O)-$CH_3$. As such, Teng et al. teaches away from the use of polymeric prodrugs.

Additionally, the claimed polymeric prodrugs require oligonucleotides modified with a bifunctional spacer group such as C2-C10 alkyl to link to a polymer via a releasable linker such as a trimethyl lock lactonization-based linker, a benzyl elimination-based linker and a bicine-based linker. None of the references relied by the Examiner teaches or suggests the specific conjugation of principal elements of the polymeric prodrugs, as claimed herein, in the order of: (1) a polymer ($R_1$); (2) a releasable linker ($L_1$); (3) a bifunctional spacer group containing C2-C10 carbons ($L_2$); and (4) an oligonucleotide ($X_1$) in Formula I of claim 1. The claimed prodrugs allow cellular uptake of oligonucleotides modified with the bifunctional spacer and modulation of target gene expression in the cells.

Teng et al. and Dandliker et al. teach, at best, non-polymeric modifications of oligonucleotides. On the other hand, Greenwald describes polymeric prodrugs. According to the teachings of the references, the artisans in the art are left to try to prepare indeterminate linkage combinations of polymeric prodrugs and non-polymeric prodrugs. The artisans would not have predicted the polymeric prodrugs containing the releasable linker and the C2-C10 bifunctional spacer conjugated in the order as required by the claimed prodrugs.

The applicants respectfully wish to draw the Examiner's attention to the requirement for the obviousness inquiry that it is impermissible within the framework of 35 USC §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts to the full appreciation of what such reference fairly suggests to one of ordinary sill in the art. *Eli Lilly v. Zenith Goldline Pharmaceuticals, Inc.*, 364 F.Supp. 2d 820, 902 (citing *In re Wesslau*, 353 F.2d 238, 241).

Thus, the applicants respectfully urge that the Examiner's position is impermissible hindsight. 35 USC §103(a) requires that a court determines whether the subject matter was obvious at the time of the invention was made and the obviousness inquiry cannot be performed using hindsight.

The references relied by the Examiner do not teach the specific linkage of the releasable linker and the C2-C10 carbon-containing bifunctional spacer between a polymer and an

oligonucleotide. The ordinary artisan would have had no reasonable expectation of success in preparing the polymeric prodrugs including the specific linkage of the releasable linker and the C2-C10 carbon-containing bifunctional spacer as required by the claimed prodrugs as amended herein.

As such, the claimed polymeric prodrugs is submitted to be fully distinguishable from the hypothetical oligonucleotides of Teng et al. modified by the teachings of Greenwald, et al. and Dandliker et al. as proposed by the Examiner.

For all of the amendments and the reasons, reconsideration and withdrawal of this ground of rejection is respectfully requested.

## E. FEES

This response is being filed with a petition for a three-month extension of time. The required fee is being submitted via credit card authorization. Thus, no further fee is believed to be required. If, on the other hand, it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to deposit account 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

## F. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that each and every one of the matters raised by the Examiner have been addressed by the present amendment and that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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